REMARKS

Claims 6-22 and 26-40 are pending in the present case. Claims 1-5 and 23-25 are withdrawn from consideration as being directed to non-elected subject matter and are cancelled herein. Claims 6-22 stand rejected under 35 U.S.C. §112, first and second paragraphs. Claims 6-12, 15, 16, 21, and 22 stand rejected under 35 U.S.C. § 102(e) and claims 6-13,16-18, and 22 stand rejected under 35 U.S.C. § 102(b). Claims 6, 14, 19, 20, and 22 further stand rejected under 35 U.S.C. § 103(a). Each of these rejections is addressed in detail below.

As a preliminary matter, Applicants note for the record that, contrary to the Office's assertion, the Declaration submitted on April 29, 2002 is in fact signed and therefore, is not defective. A copy of this declaration is submitted herewith.

Amendments

As amended, claim 6, from which the other rejected claims depend, is now directed to a method of producing an avian species that expresses a heterologous gene by contacting primordial germ cells (PGC) isolated from sex-determined gonads with a heterologous nucleic acid molecule and transferring such cells to a fertilized recipient avian egg, thereby producing an avian species that expresses a heterologous gene. Donor PGCs are obtained from gonads after sexual differentiation has begun. PGCs can be segregated by sex and can therefore be sex-matched with the recipient egg. Support for this amendment is found, for example at page 4, lines 8-14, page 5, lines 4-10, page 9, lines 16-19, page 13, lines 20-27, page 25, lines 4-5, and page 27, lines 4-10.

Support for new claims 26-29 is found, for example, at page and support for new claims 30-32 is found, for example, at page . No new material has been added by these amendments.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 6-22 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. Citing various references including Proudman et al. (Biotechnology in Animal Husbandry Vol. 5: 283-299, Renaville and Burny (eds.) Kluwer Academic Publishers; hereinafter 'Proudman'), Mohamed (Immunotechnology (1998), 4: 115-125; hereinafter 'Mohamed'), and Ivarie (Trends in Biotechnology (2003) 21: 14-19; hereinafter Ivarie), the Office states that it is unpredictable whether transferring gonadal cells transfected with a nucleic acid molecule into a recipient embryo would result in the nucleic acid molecule being introduced into the genome of an avian species. Accordingly, the Office concludes that claims 6-22 are not enabled.

On pages 3-4, the Office Action states:

> The steps of the method do not require making an avian or that the nucleic acid is incorporated into the genome any avian species; however, "introducing a nucleic acid molecule into the genome any avian species; however, "introducing a nucleic acid molecule into the genome of an avian species" bears patentable weight under enablement because each limitation must be enabled for at least one intended use.
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> In this case, introducing a nucleic acid molecule into the genome of an avian species is for making genetically altered avians having improved quality, a model of human disease, disease resistance avians or to conserve endangered species using a chicken as a "universal recipient" (pg 6, lines 7-13). However, the specification does not provide adequate guidance for one of skill to introducing a nucleic acid molecule into the genome of an avian. The specification does not provide adequate guidance for one of skill to make a avian with improved quality, that is a model of human disease, that is disease resistant or that is a "universal

recipient" because these all require introducing a nucleic acid molecule into the genome of an avian.

As amended, claim 6, from which the other rejected claims depend, is now directed to a method of producing an avian species that contains a heterologous gene by contacting sex-determined gonadal primordial germ cells (PGC) with a heterologous nucleic acid molecule and transferring such cells to a fertilized recipient avian egg, thereby producing an avian animal that contains a heterologous gene. A heterologous nucleic acid need not be integrated into the genome in order to improve the quality of an animal, confer disease resistance, or to serve as a model for human disease.

Applicants further submit that none of the cited references support the Office's conclusion that, at the time of filing, the state of the art regarding the production of transgenic avian species using transfected cells was unpredictable. For example, Proudman generally discusses various strategies for producing transgenic avian species and in fact, Proudman even cites Vick stating that transfected PGCs can successfully be used to produce transgenic offspring. Furthermore, although Ivarie states that while one of the major obstacle in making transgenic birds using transfected cells is the potential loss of germline transmission (which Applicants note is not required by the present claims), Ivarie cites Vick and points out that "[t]o date, only PGCs transduced with replication-defective ALV retrovirus have successfully generated G0 founders that in turn yielded transgenic offspring" (see page 17, column 1, fourth paragraph). In fact, regarding the Office's view that the present invention fails to be enabled because of the lack of teachings for maintaining the competency of transfected cells, Applicants note that Tsai et al. (U.S.P.N. 6,140,118), which was cited by the Examiner as § 102(e) art,

provides evidence that PGCs in culture can maintain the expression of a heterologous gene for several months. Mohamed only describes intravenous injection of a transfected cell line into laying hens for production of transgenic antibodies in eggs. The relevance of this reference is not understood.

As evidence that the claimed invention is enabled, Applicants direct the Office to page 15, lines 1-21 in which an example showing that transfected PGCs were used to produce an avian species expressing a heterologous gene. PGCs were transfected with beta-galactosidase under the control of the Cytomegalovirus promoter. Recipient chick embryos were recovered at day 10 of incubation showing expression of the test transgene beta galactosidase in the mesonephros-gonadal region. On the issue of germline transmission, Applicants even state at page 16, line 25 through page 17, line 2:

> Recipient chick embryos were recovered at day 10 of incubation showing expression of the test transgene beta galactosidase in the mesonephros-gonadal region. Polymerase chain reaction results (PCR) from gonads isolated from day 14 recipient embryos showed strong positive signals for the integration of the human lactoferin promoter sequence when donor PGCs were isolated and then transfected *in vitro*. A weaker positive signal was obtained from gonads of recipients when donor PGCs were transfected *in vivo*.

Page 20, lines 17-25 further states:

> Germline transmission of donor-derived chicks ranged from 31-78 % between experimental groups with an average transmission rate of 49% (97/198) when parent stocks were bred together. Of this, 92% of the chicks were crosses and 8 % were pure donor derived chicks. When PGCs were derived from White Leghorn embryos and transferred to colored breeds, germline transmission rates were 47 % compared to 17 % when donor PGCs from either Rhode Island Reds or Barred Plymouth Rocks were transferred to White Leghorn embryos. There was also a higher rate of transmission when the recipients received the same sex PGCs (40 %) compared to the opposite sex (7%)

In fact, regarding the Office's assertion that working examples must be presented in Applicants' specification, Applicants note that the case law does not support such a requirement. In this regard, the M.P.E.P. clearly states (emphasis added):

> *An applicant need not have actually reduced the invention to practice prior to filing.* In *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), as of Gould's filing date, no person had built a light amplifier or measured a population inversion in a gas discharge. The Court held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA) 1956)).

Rather, the case law is clear that "[t]he specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue experimentation. *In re Borkowski,* 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)." Not only does Applicants' specification provide extensive enabling details concerning the production of avian species having a heterologous gene, Applicants have described a working example in Figure 4. Moreover, transgenic chicks produced by the claimed methods were allowed to mature and were tested for the presence of the transgene following sexual maturation (see Declaration by Mr. Paul DiTullio submitted herewith). The transgene was detected in the sperm of the transgenic animals thereby providing evidence of successful incorporation into the genome and subsequent germline transmission.

For the foregoing reasons, Applicants submit that the present specification enables the currently claimed methods and provides guidance to those skilled in the art on how to carry out each and every step mentioned by the Office in making the § 112 rejection. This basis for the rejection should be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 6-22 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

The Office states that claim 6 is indefinite for failing clearly set forth the steps of the claim and because the scope of the preamble is not commensurate with the scope of the claims. Applicants have amended claim 6 to address the Office's rejection and respectfully request that this rejection be withdrawn.

With respect to claims 7-10, the Office further asserts that it is unclear what criteria Applicants use to define primordial germ cells in a cell population. Applicants submit that the metes and bounds of the percentage of PGCs in a gonadal cell population is unambiguous, the criteria and methods being defined in the specification (see page 10, lines 1-6) and known in the art for over ten years (see Yasuda et al., J. Reprod. Fert. 96: 521-528, 1992). Furthermore, Applicants note that primordial germ cells were well known in the art at the time of filing such that one skilled in the art seeking to practice the claimed invention would immediately recognized what is meant by a given percentage of primordial germ cells in a population.

Moreover, the Office states that it is unclear what system Applicants have used to stage embryos (see claims 11, 12, 15, and 16). In these claims, Applicants are referring to the Hamburger and Hamilton system. As evidence of this assertion, Applicants direct the Office's attention to page 2, lines 10-12 of the specification which clearly refer to the Hamburger and Hamilton system: "The chick embryo from which the gonadal PGCs are obtained is preferably at an embryonic stage of greater than 27 of the developing chick embryo (Hamburger Hamilton, 1951 J. Morphology 88: 49-92)." Thus, one skilled in

the art would understand that Applicants are referring to the staging system described in the cited reference.

The Office further states that the term "derived" in claims 13 and 14 is unclear. These terms no longer appear in the claims, thereby rendering this aspect of the rejection moot.

The Office also states that the term "said fertilized avian egg" in claims 15, 16, 18, 19, and 20 lacks antecedent basis. These claims have been amended as suggested by the Office and this rejection may be withdrawn.

Claims 19-21 are also rejected for reciting the term "said transfected gonadal cells." These claims have now been amended to recite "said selected cells" which find antecedent basis in claim 6 and this rejection should be withdrawn.

Furthermore, claim 6 is rejected for reciting the term "introducing a nucleic acid molecule into the genome of an avian species." Because this term no longer appears in amended claim 6, this rejection should also be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 6-12, 15, 16, and 22 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Petite (U.S.P.N. 6,33,192; hereinafter 'Petite'). Claims 6-10, 16, 21, and 22 further stand rejected under 35 U.S.C. § 102(e) as being anticipated by Tsai et al. (U.S.P.N. 6,140,118). Claims 6-13, 16, 17, and 22 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Hong et al. (Transgenic Res. (1998) 7:247-252) and claims 6-10, 13, 16-18, and 22 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Vick et al. (Proc. R. Soc. Lond. (1993) 251:179-182).

As discussed above, the present invention is now directed to the production of avian species expressing a heterologous gene using sex-determined primordial germ cells. Accordingly, based on the present invention, PGC are isolated from the gonads after sexual differentiation has begun and are therefore either male PGCs or female PGCs. Because none of the cited references disclose this limitation, all the § 102 rejections may now be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 6, 14, 19, and 22 stand rejected under 35 U.S.C. § 103(a) as being obvious over Pardue (U.S.P.N. 6,354,242; hereinafter "Pardue") in view of Petite (U.S.P.N. 6,33,192; hereinafter "Petite"). In applying this rejection, the Office states that it would have been obvious to produce an avian species as taught by Pardue using the transfected gonadal cells of Petite.

> On the issue of obviousness, the M.P.E.P. § 2143 states:
>
> To establish a *prima facie* case of obviousness, three basic criteria must be met...the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The present claims, as amended, are now directed to the production of an avian species expressing a heterologous gene using female or male primordial germ cells (PGC). As discussed above however, Petite does not teach, suggest, or even mention the production of any avian species using PCGs isolated from sex-determined gonads. Similarly, Pardue fails to disclose this limitation of the claimed invention. Absent such disclosure, the cited references, alone or in combination, do not teach every limitation of the claims and therefore, the § 103(a) rejection should be withdrawn.

Claims 6, 14, 19, 20, 22 further stand rejected under 35 U.S.C. § 103(a) as being obvious over Pardue in view of Petite and further in view of Aige-Gil (Res. Vet. Sci. 50, 1349-144). As described above, neither Petite nor Perdue teach the generation of an avian species using PGCs isolated from sex-determined gonads. Because Aige-Gil fails to cure this deficiency in Pardue and Petite, this aspect of the § 103 rejection should also be withdrawn.

CONCLUSION

Applicants submit that the claims are now in condition of allowance and such action is respectfully requested.

Enclosed is a petition of extension of time and a check in payment of the required fee. Although no fees are believed to be due, the Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 21578-007).

Respectfully submitted,

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